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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/856,374	05/21/2001	Ryuichi Morishita	Q64360	8301

7590 06/15/2004

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EXAMINER	
LI, QIAN JANICE	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,374	MORISHITA ET AL.	
	Examiner	Art Unit	
	Q. Janice Li	1632	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/6/04 & 5/11/04* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 May 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/6/04 has been entered.

The amendment and response filed 4/6/04, and the Declaration of Morishita filed 5/11/04 have been entered. Claims 13-17 have been amended, pending in the application, and under current examination.

Claim Objections

Claim 13 is objected to because the abbreviations, "HGF", "VEGF", and "HJV" should be spelled out the first time they appear in the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 13-17 are vague and indefinite because of the claim recitation "an HGF gene" and "a VEGF gene". It is unclear the meaning of the term "gene" in the context of the claims, what it encompasses or excludes, e.g. a genomic DNA, a cDNA, or a expression cassette, thus, the metes and bounds of the claims are uncertain.

Claim 14 is vague and indefinite because of claim recitation, "method for reduced blood flow". Claim as written reads on a method for reducing blood flow, whereas introducing an HGF gene into the subarachnoid space would increase blood flow as taught by the specification. Thus, the preamble is inconsistent with the method step, and the metes and bounds of the claims are uncertain.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 13-17 stand rejected and the rejection has been modified under 35 U.S.C. 103(a) as being unpatentable over *Isner et al* (US 6,121,246 or WO 97/14307), and *Morishita et al* (US Patent No. 6,248,722), in view of *Ghodsi et al* (Hum Gene Ther 1998;9:2331-40), *Yonemitsu et al* (Gene Ther 1997;4:631-8), and *Wang et al* (Biochem

Biophy Comm 1998;244:449-54), and as evidenced by *Rosengart et al* (Circulation 1999;100:468-74) and *Furlan et al* (Hum Gene Ther 1998;9:2605-17).

Claims 13-17 are drawn to a therapeutic method for cerebrovascular ischemic disorders comprising introducing an HGF and/or VEGF gene in the form of HVJ-liposome into the subarachnoid space in humans, and the specification teaches this is done by injection into the cisterna magna (page 10, line 4).

Isner et al teach treating ischemia by introducing a nucleic acid expressing a protein capable of inducing angiogenesis via direct injection into the ischemic tissue in multiple organs such as cardiac muscle cells, and in the case of cerebrovascular ischemia, the brain tissue ((column 2, lines 41-61, and paragraph bridging columns 2 & 3), wherein the angiogeneic protein is VEGF or HGF (column 3, lines9-250). *Morishita et al* teach that HGF has diverse pharmacological activities and could be used to treat many different diseases, such as nervous disorders (column 1, lines 12-26) and arterial diseases (claim 3), which encompass cerebrovascular disorders. *Morishita et al* further teach that HGF expression vector could be delivered in the form of HVJ-liposome (e.g. column 5, lines 17-36) and *in vivo* administration could be achieved via many routes such as directly into the brain tissue to selectively obtain a therapeutic effect (column 6, lines 5-14). In the working examples, *Morishita et al* illustrated the success in transducing various cells with HGF/HVJ-liposome including vascular endothelial cells in vitro, muscle cells via direct cardiac injection for treating cardiac ischemia, and articular cells via direct joint injection for repairing articular cartilage (example 1-9). Thus, the teachings of *Isner et al* and *Morishita et al* established that the state of the art pertaining

to treating ischemia with an angiogeneic protein HGF/VGF along with HVJ-liposome is high, and multiple cell types and tissue have been proven benefited from such treatment. *Isner et al* and *Morishita et al* do not particularly teach the route of injection via subarachnoid space nor illustrated adequate gene expression in the brain.

Ghodsi et al supplemented the teachings of *Isner et al* and *Morishita et al* by introducing an adenoviral vector to central nervous system via cisterna magna injection, wherein the vector expresses a therapeutic protein β-glucuronidase, wherein intense mRNA expression was seen near the site of injection, and β-glucuronidase enzyme activity could be seen throughout many parts of the brain tissue when injected via cisterna magna. More importantly, correction of β-glucuronidase deficiency was noted in both hemispheres (e.g. abstract). Thus, the teaching of *Ghodsi et al* indicated that it is well known in the art to deliver a therapeutic gene to central nervous system via subarachnoid space, and the transgene could be adequately expressed at a therapeutic level in the brain tissue to the extent that it supplemented an enzyme deficiency associated with classic lysosomal storage disease.

The teaching of *Ghodsi et al* differs from the instantly claimed invention in that the transgene carrier is an adenoviral vector, not HVJ-liposome. *Yonemitsu et al* supplemented the teachings of *Isner et al*, *Morishita et al,* and *Ghodsi et al* by comparing the gene delivery effect of adenoviral vector with that of HVJ-liposome, and advantages of using HVJ-liposome vector rather than an adenoviral vector. They teach that although a replication-deficient adenoviral vector is highly efficient in gene delivery, it could induce severe pathogenic inflammatory reaction in the host (Introduction), and

go on to teach that the HVJ-liposome based vector system is an efficient alternative to the adenoviral vector system, it can significantly and reproducibly enhance the efficacy of transgene expression, low in immunity, and superior even compared to the conventional liposome (e.g. Discussion). Thus, the teaching of *Yonemitsu et al* provides motivation to substitute the adenoviral vector system with that of HVJ-liposome system, as well as a reasonable expectation of success of using HVJ-liposome vector system in place of adenoviral vector system. Although *Yonemitsu et al* deliver a gene to airway epithelium, not brain tissue, the HVJ-liposome effect does not appear to be tissue specific because *Morishita et al* have shown that HVJ-liposome functions just as well in vascular endothelial cells, muscle cells, and articular cells.

Wang et al supplemented the teachings of *Isner et al*, *Morishita et al, Ghodsi et al,* and *Yonemitsu et al* by disclosing that both a plasmid vector and an adenoviral vector could be directly delivered into the brain tissue via intracerebroventricular injection, and that the transgene could be sufficiently expressed in the brain tissue (such as the cortex, cerebellum, brain stem, hippocampus and hypothalamus) to the extent that it caused a rapid and prolonged blood pressure-lowering effect (e.g. abstract and figs. 1a-1b). Thus, the teaching of *Wang et al* provides a reasonable expectation of success in using a plasmid vector to express a therapeutic gene in the brain tissue.

Therefore, in view of the success of HGF/VEGF-HVJ-liposome vector system in treating ischemia in multiple types of organs and cells as taught by *Isner et al, Morishita et al,* and *Yonemitsu et al;* in view of the knowledge of skill in the art regarding subarachnoid gene delivery into brain tissue as taught by *Ghodsi et al* and *Wang et al*;

in view of the success in the expression and biological effects of the delivered gene as taught by *Ghodsi et al* and *Wang et al*; and given the beneficial effect of HVJ-liposome vector system over the adenoviral vector system as taught by *Yonemitsu et al,* it would have been *prima facie* obvious to the skilled artisan at the time of filing to administer HGF/VEGF-HVJ-liposome via subarachnoid space and obtain an adequate level of HGF/VEGF expression and bring about angiogenesis for treating cerebrovascular ischemia. Further, based on successful use of the plasmid vector in gene delivery and therapy, and the knowledge that HVJ-liposome would significantly enhance a plasmid-mediated gene delivery and expression as taught by *Yonemitsu et al*, the skilled artisan would have had a reasonable expectation of success in using such for treating brain tissue ischemia. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Response to Arguments

In the 4/6/04 response, Applicants argue that one skilled in the art would not have predicted with a reasonable expectation of success that HGF/VEGF genes administered in the form of HVJ-liposome into the subarachnoid space would be effective for treatment of cerebrovascular disorders given the unpredictability of gene therapy. Applicants argue neither *Isner et al* nor *Morishita et al* teach injection into the subarachnoid space, nor enable gene transfer to central nervous system. *Ghodsi et al* do not teach use of the HGF gene or VEGF gene in the form of HJV-liposomes or treating cerebrovascular disorder, one skilled in the art would not have been motivated

to combine the references with a reasonable expectation of success in achieving the claimed invention. Applicants filed a Declaration stating that a person skilled in the art could not have reasonably expected that injection of VEGF and HGF genes into the subarachnoid space would result in significant levels of protein expression in the brain as achieved by the present invention given the poor efficiency of gene transfection in the central nervous system, and citing *Saitoh et al* as support.

The argument has been fully considered but they are not persuasive for reasons set forth above and following.

1. The claims do not have any limitation concerning the levels of protein expression, thus, the levels of gene expression in the brain which resulted in a therapeutic effect as taught by *Ghodsi et al* and *Wang et al* are considered to be adequate, thus meet claim limitation.
2. The effect of HGF and VEGF are known to promote endothelial cell growth and angiogenesis, are known to be functional in many different organs and tissues, and have achieved success in ischemic animal models in various organs such as taught by *Isner et al, Morishita et al, Yonemitsu et al,* and *Rosengart et al* (Circulation 1999;100:468-74). Nothing on record indicates that such effect would not exert in the brain tissue. Moreover, it is noted that both HGF and VEGF induce angiogenesis by promoting the growth of vascular endothelial cells, thus, as long as they are delivered to the vascular system of the brain

via subarachnoid space, an expectation that HGF/VEGF would bring about therapeutic angiogenesis is reasonable.

3. Significant levels of transgene expression in brain tissue and subsequent biological effects have been observed for different types of therapeutic proteins such as human tissue kallikrein gene (*Wang et al*), β-glucuronidase (*Ghodsi et al*), and Interleukin-4 (*Furlan et al*), nothing on record indicates that such expression and effect would not occur for VEGF or HGF.

4. It is well known in the art that HVJ-liposome could significantly enhance the efficacy of a plasmid and superior than conventional liposome carrier as taught by *Yonemitsu et al* (see also *Yonemitsu et al*, Int J Oncol 1998;12:1277-85), and since using a plasmid vector alone has achieved certain levels of gene expression in the brain and subsequently obtained a therapeutic effect as taught by *Wang et al*, when combined with the HVJ-liposome, a significant enhancement in gene delivery and expression is reasonably expected. Even though *Saitoh et al* stated that the efficacy of HVJ-liposome in the brain is unknown, given its success in other tissues, and given the success of *Wang et al* and *Ghodsi et al*, the success of HGF/VEGF-HVJ-liposome would be reasonably expected in the brain.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Amy Nelson** can be reached on 571-272-0804. The fax numbers for the organization where this application or proceeding is assigned are **703-872-9306**.

Any inquiry of formal matters can be directed to the patent analyst, **Dianiece Jacobs**, whose telephone number is (571) 272-0532.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist **Rena Jones** whose telephone number is **571-272-0571**.

JANICE LI
PATENT EXAMINER

Q. Janice Li
Patent Examiner
Art Unit 1632

QJL
June 14, 2004